

REMARKS

Independent claims 1, 68 and 69 and the claims which depend thereon have been canceled to reduce costs. Claim 91 has been amended to recite specific classes of diseases and claims 107 and 121 have been amended to recite the treatment of cancerous cell growth mediated by raf kinase.

Claim Rejections Under 35 U.S.C. § 112, first paragraph

Applicants maintain that all pending claims clearly comply with the written description requirement of 35 U.S.C. § 112, first paragraph. The phrases objected to which define the compounds of Formula I such as “substituted moiety of up to 40 carbon atoms” do not appear in any of the pending claims. In addition, no evidence has been presented that these phrases failed to provide an adequate written description of the compounds of Formula I used in the methods claimed herein. Therefore, there is no basis for finding the compounds used in the claimed methods inadequately described. In fact, there is full written description of all mentioned phrases, even under the appropriate cited case law.

The treatment of “cancerous cell growth mediated by raf kinase” and “treatment of carcinomas, myeloid disorders and adenomas” are described at page 2, lines 10–20 of the specification. Here it is stated that “the present invention provides compounds which are inhibitors of the enzyme raf kinase” and that “the inhibitors are useful in pharmaceutical compositions for human and veterinary use where inhibition of the raf kinase pathway is indicated, e.g., in the treatment of tumors and/or cancerous cell growth mediated by raf kinase.” It is further described that “the compounds of the invention are useful in treating cancers, including solid cancers such as, for example, carcinomas (e.g., of the lungs, pancreas, thyroid, bladder or colon), myeloid disorders (e.g., myeloid leukemia), or adenomas (e.g., villous colon adenoma).” No evidence has been presented that these descriptions are

ambiguous or inadequate in any way in describing the conditions to be treated by the present invention.

As discussed in the previous response, the specification identifies publications which associate the inhibition of the raf kinase signal pathway with 1) the reversion of transformed cells to the normal growth phenotype, 2) blocked cell proliferation in membrane associated oncogenes and 3) correlation with the inhibition of a growth of a variety of tumor types. Based on the disclosure in the specification as well as the conventional knowledge of skilled artisans, the phrase “the treatment of cancerous cell growth mediated by raf kinase” adequately describes the conditions intended to be treated in a manner sufficient to be recognized by one skilled in the art. Such a description satisfies the statute. In addition, the phrases “treatment of solid cancers” and “treatment of carcinomas, myeloid disorders or adenomas,” expressly describe specific classes of diseases, well known to those skilled in the art. No evidence has been presented to show this language is ambiguous or encompasses subject matter beyond the scope of the invention. Based on the disclosure within the specification and the conventional knowledge regarding raf kinase inhibition, one skilled in the art would clearly understand the scope of the terms used in defining the conditions to be treated with the compounds of the invention.

Applicants maintain the language employed in the pending claims is not inconsistent with the holdings in *Regents of the University of California v. Eli Lilly and Enzo Biochem, Inc. v. Gen-Probe*, cited by the Examiner. Evidence has yet to be presented showing that the method claims are imprecise in defining the conditions to be treated. As described in the specification, the correlation of raf inhibition and the treatment of certain diseases was known at the time of the invention. *Enzo* recognized that functional characteristics such as these can provide a complete disclosure where there is a known correlation. No evidence has been presented to the contrary.

In responding to applicants' previous arguments, the Examiner alleges that the publications Kolch et al. and Monia et al. fail to support the teachings of the instant specification. The Examiner has focused narrowly on the data provided by Kolch and Monia and not the overall teachings of these references as to what the data show. For example, the teachings within the abstract of Monia state that "These studies strongly suggest that antisense inhibitors targeted against the C-raf kinase may be of considerable value in antineoplastic agents that display activity against a wide spectrum of tumor types at well-tolerated dosages."

Moreover, as to the chemical compounds encompassed, the cited case law is especially inopposite. None of the expressions encompass genera which would pose any problem for skilled workers to enumerate large numbers of encompassed species, in contrast to *Lilly* and *Rochester*. As to the biological functional language at issue, there also is no problem at least because species of diseases are identified and a functional correlation between them and other diseases is disclosed by virtue of the conventional terms such as solid tumors, etc., these cannot have the supposed written description defect of *Lilly*, *Rochester*, etc., precisely because they are so well known. Identification of conventional information is not required for any reason. Therefore, applicants maintain the pending claims satisfy the written description requirement of 35 U.S.C. § 112, first paragraph.

Enablement

Applicants maintain all pending claims clearly satisfy the enablement requirement of 35 U.S.C. § 112, first paragraph. No evidence has been presented to support the rejection. The Examiner still relies on the *Wands* factors and allegations that the claims are very broad with respect to the compounds used. However, the compounds of Formula I, all fall within a class of ureas having a certain skeletal structure of cyclic moieties defined by "B" of the

Formula I and the bridged cyclic structure of "A." These ureas also require one of three substituents on the moiety L¹. No evidence has been presented that compounds with these features will not perform in the methods claimed herein and therefore, the rejection under 35 U.S.C. § 112 is not supported by the allegations regarding the scope of compounds encompassed by Formula I.

There is also an allegation that the specification does not provide guidance in treating the cancers encompassed by the claims. Contrary to this allegation, the specification does provide guidance on how to prepare pharmaceutical compositions and how to administer them on page 10–14 of the application. The specification also provides dosage ranges for various methods of administration on page 13. The Examiner alleges that the Stein et al. reference shows that many types of cancers involve different cellular mechanisms and thus different treatment protocols. As indicated above, applicants provide sufficient guidance with respect to dosages and methods of administration such that one skilled in the art can modify the protocol by routine experimentation. Such routine experimentation is not undue.

Given the extent of the disclosure provided, it would have most involved routine experimentation, if any at all, for one skilled in the art to treat any one of the recited cancers with a compound of this invention. Even absent the specification disclosure as discussed above, the rejection is clearly deficient under general controlling case law. The courts have placed a burden on the PTO to provide evidence shedding doubt on the disclosure that the invention can be made and used as stated. See example *In re Marzocchi*, 439 F.2d 220, 169 USPQ 367 (CCPA 1971).

The Examiner finds the specification is enabling only for the *in vitro* treatment of tumor cell lines HCT-116 AND DLD-1. However, it is not necessary to provide dedicated assays for each form of cancer encompassed by the claims, as is suggested by this finding. See, for example, *In re Howarth*, 654 F.2d 105, 210 USPQ 689 (CCPA 1981); and *In re Gay*,

309 F.2d 769, 135 USPQ 311 (CCPA 1962). There is no requirement that applicant provide any working examples relating to the treatment of every claimed disease to satisfy the statute. See, for example, *In re Angstadt*, 537 F.2d at 502–503, 190 USPQ 214 (CCPA 1976) (which held that applicants, “are not required to disclose every species encompassed by the claims even in unpredictable art.”)

The PTO has failed to meet its burden of establishing that the disclosure does not enable one skilled in the art to make and use the compounds recited in the claims. Instead of evidence of non-enablement, the Examiner cites the lack of predictability of the efficacy of chemotherapeutic agents in the field of the cancer art in requiring additional working examples. The Examiner is requiring that the applicant meet the clinical standards as set forth by the FDA to satisfy that enablement requirement under 35 U.S.C. § 112, first paragraph. This is clearly not the intention of the statute. As stated in *In re Anthony*, 414 F.2d 1383, 162 USPQ 594 (CCPA 1969), “approval by the FDA, is not a prerequisite for the patenting of a new drug.” A lack of predictability can be addressed by routine experimentation which is permissible under the statute. A considerable amount of experimentation is permissible if it is merely routine or if the specification in question provides a reasonable amount of guidance with respect to direction which the experimentation should proceed (see *In re Wands* cited by the Examiner). An applicant is not required to test the claimed compounds in their final use. As stated in *In re Branna*, 51 F.3d 1516, 34 USPQ 1436 (Fed. Cir. 1995), with respect to the utility requirement, “If the courts were to require Phase II testing in order to prove utility for pharmaceutical inventions, the associated costs would prevent many companies from obtaining patent protection on promising new invention thereby eliminating an incentive to pursue the research development of potential cures in many crucial areas.” The same rationale applies to meeting the enablement and disclosure requirements of 35 U.S.C. § 112, first paragraph. The

specification provides more than it needs, for example, *in vitro* raf kinase assays and *in vivo* assays. In similar fashion, one of ordinary skill in the art by performing the same or similar tests can by routine experimentation determine the activity levels of each of the claimed compounds in treating various cancers.

For the reasons discussed above, applicants submit all pending claims satisfy the requirements of 35 U.S.C. § 112, first paragraph.

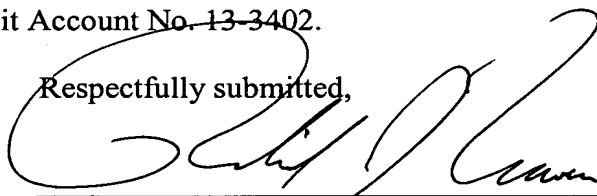
Obviousness-Type Double-Patenting

These provisional rejections will be addressed once claims herein are otherwise in condition for allowance.

In view of the above, favorable reconsideration is courteously requested. If there are any remaining issues which can be expedited by a telephone conference, the Examiner is courteously invited to telephone counsel at the number indicated below.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. ~~13-3402~~.

Respectfully submitted,



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